

Jan., 1939

ANTISPASMODICS

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184° (19 mm. pressure), and 23 g. of methyl- β -cyclohexylethylamine, b. p. 89–90° (14 mm. pressure).

In a second procedure 56.4 g. of methyl- β -cyclohexylethylamine, 76.4 g. of β -cyclohexylethyl bromide and 42.4 g. of anhydrous sodium carbonate was heated in an oil-bath at 145–150° for twenty hours; yield of methyldi-(β -cyclohexylethyl)-amine 45 g.

The hydrochlorides were obtained by treatment of an ether solution of the base with hydrogen chloride; in the case of compound 31 the base was dissolved in carbon tetrachloride.

Some of the amine hydrochlorides, such as those of compounds 5, 9, 23, 30 and 31, are not very soluble in water.

The nitrate of methyldi-(β -cyclohexylethyl)-amine precipitated in crystalline form when the calcd. amount of concd. nitric acid was added to the base dissolved in ether; m. p. 158–159° after recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_{17}H_{31}O_3N_2$: N, 8.92. Found: N, 8.84.

Upon addition of gold chloride solution to an aqueous solution of methyldi-(β -cyclohexylethyl)-amine hydrochloride the yellow, crystalline chloroaurate precipitated; m. p. 166–167° after recrystallization from dilute alcohol.

Anal. Calcd. for $C_{17}H_{31}N \cdot HCl \cdot AuCl_2$: Au, 33.35. Found: Au, 33.37.

Methyldi-(β -benzoylethyl)-amine (Compound 29).—By a slight modification of the procedure of Mannich and Heilner,⁶ namely, interaction of acetophenone, trioxymethylene and methylamine hydrochloride, the yield of the desired amine was increased from 31 to 58%.

(6) Mannich and Heilner, *Ber.*, 55, 362 (1922).

After removal of the alcohol from the reaction mixture the residue was heated on a steam-bath for twelve hours, the mixture of crystals and oil treated with ether and the undissolved, crystalline hydrochloride washed with alcohol; the hydrochloride weighed 32.3 g. The combined ether and acetone solutions were placed in an evaporating dish, the solvents removed on a steam-bath and the residue heated for twelve hours. The mixture of oil and crystals was washed with ether and acetone as described above; an additional 6.2 g. of amine hydrochloride was obtained.

Treatment of the salt, dissolved in dilute alcohol, with sodium hydroxide yielded the oily base which soon crystallized; m. p. 141–142°.

The hydrochloride precipitated when the base, dissolved in carbon tetrachloride, was treated with hydrogen chloride. The base may also be dissolved in benzene, hydrogen chloride passed into the solution and the hydrochloride precipitated by the addition of dry ether; m. p. 191–192°.

Anal. Calcd. for $C_{19}H_{27}O_2NCl$: Cl, 10.69. Found: Cl, 10.43.

Summary

A number of new secondary and tertiary amines which contain a cycloalkylalkyl or an arylalkyl group have been described.

It was found that most of the amines exhibit antispasmodic activity to some extent and that several of them are very potent in this respect.

(7) Mannich and Heilner (*ibid.*, 55, 362 (1922)) reported 142°.

(8) Mannich and Heilner (Ref. 7) as well as Bermejo and Blas (*Chem. Zentr.*, 101, I, 554 (1930)) reported 162°.

ANN ARBOR, MICHIGAN

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. II¹

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Since no extensive, systematic study seems to have been published which might permit some conclusion to be reached relative to a relationship between chemical structure and antispasmodic activity, we have prepared a large number of amines which have been tested pharmacologically, usually in the form of their hydrochlorides, by Dr. C. W. Geiter in the Frederick Stearns and Company Laboratories.

It cannot be stressed too emphatically that no trustworthy, broad generalization can be drawn except on the basis of data obtained from the examination of hundreds of compounds. How-

ever, as far as the amines described in this and the preceding paper³ are concerned, the following statements may be made from the data now available.

An examination of the cyclohexylalkyl compounds of the series $CH_3N[(CH_2)_x-C_6H_{11}]_2$ in which $x = 1, 2, 3$ or 4 showed that all of the compounds appear to be weak in activity except methyldi- β -cyclohexylethylamine, $CH_3N[(CH_2)_2-C_6H_{11}]_2$, which is a strong antispasmodic.

A second series may be represented by the general formula $RN(CH_2-CH_2-C_6H_{11})_2$ in which R = hydrogen, methyl, ethyl, propyl, isopropyl, butyl, amyl, heptyl, phenyl, β -cyclohexylethyl, allyl, cyclohexyl, benzyl or β -hydroxyethyl. The first five compounds in this group were found to be

(3) Blicke and Monroe, *This Journal*, 61, 91 (1939).

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by F. B. Zienty in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

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TABLE I
AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides of the amines were recrystallized as follows: compounds 24, 28 and 29 were recrystallized from carbon tetrachloride; compounds 14, 25 and 26 from 1,4-dioxane; compounds 4, 7 and 12 from ethyl acetate; compound 5 from acetone; compound 11 from alcohol; compound 9 from a mixture of absolute alcohol and ethyl acetate; compounds 1, 2, 6 and 10 from a mixture of alcohol and acetone; compound 13 from a mixture of acetone and petroleum ether (30–40°); compounds 3, 8, 15, 16 and 27 were precipitated from a carbon tetrachloride solution by addition of dry ether; compound 30 was precipitated from an alcohol solution by addition of dry ether; the chloroaurate of compound 21 was recrystallized from dilute alcohol.

| Amine (secondary) | Antispasmodic activity | Prepared from | B. p. of fraction used °C. | Mm. | M. p. °C. | Amine hydrochloride | | |
|---|------------------------|---|----------------------------|-----------------|----------------------|---|----------------------|-------|
| | | | | | | Formula | %Cl Calcd. | Found |
| 1 Methylcyclohexylmethyl | (Stimulant) | Methylamine | 65–66 | 13 | 193–194 | C ₈ H ₁₇ NCl | 21.67 | 21.53 |
| 2 Ethylcyclohexylmethyl | (Stimulant) | Ethylamine | 72–73 | 12 | 249–250 | C ₉ H ₁₉ NCl | 19.96 | 19.87 |
| 3 β -Hydroxyethyl- β' -cyclohexylethyl | Inactive | β -Hydroxyethylamine | 138–142 | 7 | 163–164 | C ₁₀ H ₁₉ ONCl | 17.08 | 16.94 |
| 4 Propyl- β -cyclohexylethyl | (Stimulant) | Propylamine | 108–107 | 13 | 266–267 | C ₁₁ H ₂₁ NCl | 17.24 | 17.10 |
| 5 Isopropyl- β -cyclohexylethyl | Weak | Isopropylamine | 102–104 | 10 | 199–200 | C ₁₀ H ₂₁ NCl | 17.24 | 17.02 |
| 6 Amyl- β -cyclohexylethyl | Weak | Amylamine | 109–115 | 7 | 266–266 | C ₁₁ H ₂₃ NCl | 15.17 | 15.09 |
| 7 Heptyl- β -cyclohexylethyl | Active | Heptylamine | 135–140 | 7 | 242–243 | C ₁₁ H ₂₃ NCl | 13.55 | 13.47 |
| 8 Phenyl- β -cyclohexylethyl | Weak | Aniline | 170–173 | 9 | 122–123 | C ₁₀ H ₁₅ NCl | 14.79 | 14.71 |
| 9 Di- β -cyclohexylethyl | Active | β -Cyclohexylethylamine ^a | 168–173 | 8 | 245–246 | C ₁₀ H ₁₉ NCl | 12.95 | 12.65 |
| 10 α -Cyclohexylethyl- β' -cyclohexylethyl | Active | α -Cyclohexylethylamine ^b | 165–166 | 10 | 222–223 | C ₁₁ H ₂₃ NCl | 12.95 | 12.87 |
| 11 Di- α -cyclohexylethyl ^c | Weak | ... | 140–142 | 4 | 304–305 | C ₁₁ H ₂₃ NCl | 12.95 | 12.93 |
| Amine (tertiary) | | | | | | | | |
| 12 Methylcyclohexyl | Weak | Dicyclohexylamine | 131–133 | 13 ^d | 193–194 | C ₁₁ H ₂₃ NCl | 15.30 | 15.14 |
| 13 Amyldicyclohexyl | Weak | Dicyclohexylamine | 178–181 | 20 | 113–114 | C ₁₇ H ₃₅ NCl | 12.32 | 12.31 |
| 14 Methylcyclohexylmethyl | Weak | Methylamine | 124–125 | 4 | 240–241 | C ₈ H ₁₇ NCl | 13.66 | 13.55 |
| 15 Ethylcyclohexylmethyl | (Stimulant) | Ethylamine | 149–153 | 12 | 137–138 | C ₉ H ₁₉ NCl | 12.95 | 12.90 |
| 16 β -Hydroxyethyl-di- β' -cyclohexylethyl | Inactive | β -Hydroxyethylamine | 190–193 | 5 | 112–113 | C ₁₁ H ₂₃ ONCl | 11.16 | 11.22 |
| 17 Di- β -hydroxyethyl- β' -cyclohexylethyl | Inactive | Di- β -hydroxyethylamine | 177–179 | 7 | Oil ^e | ... | ... | ... |
| 18 Propyl-di- β -cyclohexylethyl | Active | Propylamine | 160–165 | 7 | Oil | C ₁₀ H ₂₁ N | N, ^f 5.02 | 4.96 |
| 19 Isopropyl-di- β -cyclohexylethyl | Active | Isopropylamine | 171–174 | 7 | Oil | C ₁₀ H ₂₁ N | N, ^f 5.02 | 5.24 |
| 20 Butyl-di- β -cyclohexylethyl | Weak | Butylamine | 176–178 | 7 | Oil | C ₁₀ H ₂₃ N | N, ^f 4.78 | 4.68 |
| 21 Dibutyl- β -cyclohexylethyl | Weak | Dibutylamine | 124–127 | 5 | 127–128 ^g | C ₁₈ H ₃₉ NCl ₃ Au | Au, 34.04 | 34.01 |
| 22 Amyl-di- β -cyclohexylethyl | Weak | Amylamine | 178–181 | 7 | Oil | C ₁₁ H ₂₅ N | N, ^f 4.56 | 4.70 |
| 23 Heptyl-di- β -cyclohexylethyl | Inactive | Heptylamine | 197–202 | 6 | Oil | C ₁₁ H ₂₅ N | N, ^f 4.18 | 4.21 |
| 24 Allyl-di- β -cyclohexylethyl | (Stimulant) | Allylamine | 170–172 | 5 | 137–138 | C ₉ H ₁₉ NCl | 11.30 | 11.31 |
| 25 Cyclohexyl-di- β -cyclohexylethyl | (Stimulant) | Cyclohexylamine | 180–193 | 5 | 166–167 | C ₁₁ H ₂₃ NCl | 9.97 | 10.09 |
| 26 Dicyclohexyl- β -cyclohexylethyl | Active | Dicyclohexylamine | 180–182 | 5 | 172–173 | C ₁₃ H ₂₇ NCl | 10.82 | 10.83 |
| 27 Phenyl-di- β -cyclohexylethyl | Weak | Aniline | 213–218 | 5 | 149–150 | C ₁₁ H ₁₅ NCl | 10.14 | 9.94 |
| 28 Benzyl-di- β -cyclohexylethyl | (Stimulant) | Benzylamine | 207–210 | 5 | 142–143 | C ₁₁ H ₁₉ NCl | 9.75 | 9.73 |
| 29 Tri- β -cyclohexylethyl | Weak | Compound 9 | 200–203 | 6 | 233–234 | C ₁₁ H ₂₃ NCl | 9.24 | 9.26 |
| 30 Methyl-di- α -cyclohexylethyl | Weak | Compound 11 | 167–169 | 12 | 179–180 | C ₁₇ H ₃₅ NCl | 12.32 | 12.40 |

^a Coleman and Adams, *THIS JOURNAL*, 54, 1983 (1932). ^b Leithe, *Ber.*, 65, 665 (1932). ^c Obtained as a by-product in the preparation of the corresponding primary amine. ^d Prepared by different methods Skita and Berendt [*Ber.*, 52, 1528 (1919)] reported 265°; Hiers and Adams [*ibid.*, 59, 167, 170 (1926)] found 140–141° (26 mm.). ^e The hydrochloride of the dibenzoate is described above. ^f Analysis of the base. ^g Melting point of the chloroaurate.

active,⁴ the butyl and amyl derivatives weakly active and the heptyl compound inactive; the phenyl and β -cyclohexylethyl derivatives are weak antispasmodics; the allyl, cyclohexyl and benzyl compounds are stimulants and the β -hydroxyethyl-di- β' -cyclohexylethylamine is inactive.

In a series of secondary amines which conform to the general formula RN(H)(CH₂-CH₂-C₆H₁₁)₂ in which R = propyl, isopropyl, amyl, heptyl, phenyl, β -cyclohexylethyl or α -cyclohexylethyl only the

(4) In this series of papers the term active is used to denote that the compound is a strong antispasmodic and the term inactive to indicate a very low degree of activity.

heptyl, β -cyclohexylethyl and α -cyclohexylethyl compounds are active.

Dicyclohexylamine, methyl- and amyldicyclohexylamine exhibit weak activity but β -cyclohexylethyl-dicyclohexylamine is decidedly active.

A few compounds of the type CH₃N(CH₂-CH₂-R)₂ were prepared in which R represents phenyl, phenoxyethyl, cyclopentyl or benzoyl; the first two compounds proved to be active, the last two weak.

It is interesting to compare the activity of an amine which contains an α -cyclohexylethyl group with that of an isomeric β -cyclohexylethyl com-

pound. Di- α -cyclohexylethylamine was found to be weak while di- β -cyclohexylethylamine is active; the mixed amine α -cyclohexylethyl- β' -cyclohexylethylamine is active. Furthermore, methyl-di- α -cyclohexylethylamine is weak while the isomeric methyl-di- β -cyclohexylethylamine is active.

Experimental Part

The amines, except those described below, were prepared by the general methods outlined previously.³

β -Cyclohexylethyl Alcohol.—Several modifications have been made in the procedure of Hiers and Adams.⁴

Cyclohexylmagnesium bromide was prepared from 72 g. of magnesium, 489 g. of bromocyclohexane and 1000 cc. of ether in a 3-liter three-necked flask fitted with a stirrer, condenser and dropping funnel. The solution of the Grignard reagent was stirred, cooled to 15–20° and maintained at this temperature while 220 cc. of liquid ethylene oxide was added dropwise. The temperature of the mixture was then allowed to rise to that of the room, 500 cc. of dry benzene was added, the mixture heated to 70°, maintained at this temperature for one hour and then treated with ice and sulfuric acid. The product which boiled at 105–110° (20 mm.) was used; yield 197 g. or 51% of the calcd. amount.

Methyldicyclohexylamine (No. 12).—A mixture of 18.1 g. of dicyclohexylamine and 15 g. of 38% formaldehyde solution was heated on a steam-bath for ten hours. The amine was extracted with ether, the extract dried and the solvent removed; yield of pure product 16 g.

Hydrochloride of the Dibenzoyl Derivative of Di- β -hydroxyethyl- β' -cyclohexylethylamine.—To 4.3 g. of di- β -hydroxyethyl- β' -cyclohexylethylamine (compound 17), dissolved in 10 g. of pyridine, there was added 5.6 g. of benzoyl chloride dissolved in 10 cc. of benzene. The mixture was refluxed for one hour on a steam-bath, filtered, the solvents removed, the oily residue washed with water and then extracted with ether. The extract was dried and treated with hydrogen chloride whereupon the hydrochloride precipitated. The oily hydrochloride was washed with absolute ether, dissolved in a small amount of ethyl acetate and precipitated by the addition of dry ether; the oily precipitate soon crystallized. It was dissolved in 50% alcohol and the solvents allowed to evaporate partially at ordinary temperature; m. p. 137–138°.

Anal. Calcd. for $C_{24}H_{44}O_4NCl$: Cl, 7.71. Found: Cl, 7.84.

α -Cyclohexylethylamine.—A mixture of 126 g. of methyl cyclohexyl ketone⁵ and 189 g. of ammonium formate was placed in a 500-cc. Claisen flask, attached to an inclined condenser, and a few pieces of porous plate added. The mixture was heated with a thermometer immersed in the liquid. When the temperature reached 120° prac-

tically all of the formate had melted, two layers were formed and the mixture foamed slightly. The foaming increased as the temperature was raised. At 140° water and methyl cyclohexyl ketone began to distil. The material became homogeneous at 155°. When the mixture reached a temperature of 180° the heating was interrupted and the upper ketone layer in the distillate was separated and returned to the Claisen flask. The mixture was heated at 180–185° until distillation of the ketone became slow. The ketone which had distilled into the receiver was again returned to the Claisen flask and the mixture heated three hours longer.

The material was cooled, washed with about 200 cc. of water and returned to the reaction flask. The wash water was extracted three times with 30-cc. portions of benzene and the extracts poured into the reaction flask. After the addition of 125 cc. of concd. hydrochloric acid heat was applied gradually until the benzene was removed, the mixture boiled for one hour, cooled and extracted with benzene to remove unchanged ketone. Excess alkali was added, the oil extracted with ether, the extract dried with fused sodium sulfate and the solvent removed; b. p. 66–67° (14 mm.).⁷

The hydrochloride precipitated when hydrogen chloride was passed into an ether solution of the base; m. p. 237–238°⁸ after recrystallization from a mixture of alcohol and acetone. The salt is very soluble in water.

Anal. Calcd. for $C_8H_{19}NCl$: Cl, 21.67. Found: Cl, 21.52.

Di- α -cyclohexylethylamine (No. 11).—In the preparation of the primary amine described above there was obtained 23 g. of di- α -cyclohexylethylamine.

The hydrochloride precipitated when an ether solution of the base was treated with hydrogen chloride. The salt is not very soluble in water.

Methyl-di- α -cyclohexylethylamine (No. 30).—Seven grams of di- α -cyclohexylethylamine hydrochloride, ten drops of concd. hydrochloric acid and 7.5 g. of formalin were refluxed for ten hours, the mixture made alkaline and extracted with ether. The solvent was removed from the dried extract and the residue distilled; b. p. 167–169° (12 mm.); yield 4.6 g.

The hydrochloride, obtained in the manner described above, is very soluble in water.

Summary

A number of secondary and tertiary amines have been prepared which contain alkyl, cyclohexyl, α -cyclohexylethyl or β -cyclohexylethyl groups. Some of these compounds have been found to be strong antispasmodics.

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(7) Leithe [*Ber.*, 66, 665 (1932)] prepared the amine by hydrogenation of α -phenylethylamine and Wallach [*Ann.*, 358, 192 (1912)] by reduction of the nitrosochloride of ethyldene-cyclohexane but neither investigator reported a boiling point.

(8) Leithe⁷ reported 242°.

(5) Hiers and Adams, *THIS JOURNAL*, 48, 1091 (1926).

(6) Bouveault, *Bull. soc. chim.*, [3] 29, 1050 (1903).